projects. In fact, several ACME users have written their own. Since the data bases have been established independently, the result is a variety of data base designs and a duplication of information and retrieval methods. A future system should include a unified patient data base, serving all patient care and related research programs of the Stanford Hospital and Medical School. The data base structure might be designed as a master file of common patient elements and a number of subfiles for information unique to a medical descipline. Retrieval might be along commonly used paths of the data base structure or it may be unpredictable. That is, the questions cannot be determined in advance. Consequently, the retrieval mechanism should honor both predetermined and unpredictable requests. One implementation scheme would incorporate the generalities of the PL/ACME language with new commands for executing predefined functions.

c. Realtime Data Collection

ACME service in this area was a pioneering effort at the time it was implemented. For today's technology, ACME's data rate capability is low and incapable of handling many applications. The 1800 can accomodate an aggregate of only 10,000 samples per second, and many users claim difficulty whenever aggregate data rates exceed 2,500 samples per second. Users must obtain realtime input/output lines from an ACME operator. This service should be automated. The 1800 is used only as a traffic control device and not for any pre-processing of data. The Model 50's bulk core is 8 microsecond core and this is a fundamental limitation in the speed of the system. One user in Nuclear Medicine recently proposed purchase of a dedicated small machine with disk and tape peripherals to handle bursts of 40,000 samples per second. The role of the "smart" or HIQ terminals applies to this realtime data collection requirement. ACME must determine the best way to meet the need for this type of service. A small machine pool may be a solution, especially if a few of these units can be equipped with disk and/or tape.

4. I/O Devices

Voice Drum. A private corporation gave Stanford one voice drum. We are eager to find a potential user of the voice drum so that we can work with him to develop this hardware. The drum has a limited vocabulary of 50 words. The hardware interfacing the voice drum to the PDP-11 should be finished by the end of the current fiscal year. We anticipate using voice output for a warning system or in other situations to call attention to a typewriter or graphics terminal.

Tape Cassette. We would like to explore the use of the tape cassette for storage of user data. Users might find that tape cassettes could replace disk storage for many applications. We would like to make it possible for the user to enter data on line, analyze it to some extent, record it on tape cassettes, and retrieve it for future analysis as needed. The potential reliability added by collecting all data on tape cassette at the time of data input is also significant.

Alphanumeric Displays. The alphanumeric displays added to ACME for the Drug Interaction Program during this past year have been interfaced to the PDP-11 which in turn has been interfaced to the 360/50. ACME software has been and is being modified to better support these devices. For a significant number of ACME users (10-20) alphanumeric displays would be better than the current 2741 typewriter terminals because they are quieter, offer one page at a time rather than one line at a time, and are very convenient especially for fixed formats of data entry. We consider special support for this type of hardware highly desirable. Such support may include new commands for handling full pages of data and revise editing features, and other commands designed to take advantage of the 2-dimensional nature of CRT's.

PART II. ACME USER DEVELOPMENTS

IV. PROJECT DESCRIPTIONS: CORE RESEARCH AND MAJOR USERS

A. Core Research Descriptions

During the past year ACME has identified several user projects which we consider core research application work under the ACME grant. One specific example is Dr. Stanley Cohen's drug interaction project. For this project ACME pays for the computing services including some of the programming effort.

Another kind of core research application consists of Dr. Lederberg and Dr. Feigenbaum's DENDRAL project. The DENDRAL project intends to pay for its computing services according to the grant request, but ACME will support new systems work specifically for DENDRAL.

A third type of core research is one in which ACME pays for all computing services and the user pays for all other associated costs. The projects of Dr. Bellville (G_SWANSO.THESIS) and Dr. Sussman fall into this category. Dr. Sussman developed a Clinical Laboratory Information System on ACME. When development was complete, he requested financial support from the Hospital for its operation. Therefore, the LABSYS project has been completed as a core research task.

IV. PROJECT DESCRIPTIONS: CORE RESEARCH AND MAJOR USERS

Cross Reference Core Research Table

Principal Investigator	Project	ACME User	Pageminutes	File Storage	Project Description Page
Bellville, J.	THESIS	Swanson, G.	770,609	27,342	31
Cohen, S.	DRUGALRT	Cohen, S.	492,858	20,141	32
Feigenbaum, E. Lederberg, J. Djerassi, C.	DENDRAL	Reynolds, W.	55,220	300	33-36
Feigenbaum, E. Lederberg, J. Djerassi, C.	DENDRAL	Ross, R.	128,176	2,125	33-36
Feigenbaum, E. Lederberg, J. Djerassi, C.	DENDRAL	Stefik, M.	216,957	2,088	33-36
Feigenbaum, E. Lederberg, J. Djerassi, C.	DENDRAL	Stillman, R.	88,896	400	33-36
Feigenbaum, E. Lederberg, J. Djerassi, C.	DREAMS	Reynolds, W.	346,971	18,445	33-36
Feigenbaum, E. Lederberg, J. Djerassi, C.	DREAMS	Stillman, R.	199,650	10,430	33-36
Feigenbaum, E. Lederberg, J. Djerassi, C.	CHEM	Ross, R.	633,855	15,123	33-36
Feigenbaum, E. Lederberg, J. Djerassi, C.	GAME	Bacon, V.	1,030,239	32,850	37
Sussman, H.	LABSYS	Sussman, H.	43,083	182	38
Sussman, H.	LABENG	Sussman, H.	924	9	39

IV. PROJECT DESCRIPTIONS: CORE RESEARCH AND MAJOR USERS

Respiratory Studies

Name: Swanson, G. (P.I.: Bellville, W.) Project: THESIS

Department: Anesthesia

Project Description: The precise interpretation of the drug action mechanism on the human respiratory system is critically important for the evaluation of new pain relieving drugs. The improvement of analgesics and antagonists depends in part on the precision and specificity of this interpretation. The classical experimental methods are restricted to assessing drugs in terms of an integrated respiratory effect. One method of improving the specificity is to model the respiratory system mathematically and interpret a drug effect as a parameter change. This project involves the development of an experimental computer-aided instrumentation system for accumulating and interpreting human respiratory response data in terms of a mathematical model. The model quantifies the function of the peripheral and central chemoreceptors, and the effect of oxygen tension on carbon dioxide response. A parameter estimation scheme estimates the model parameters from input-output respiratory data. The model input (experimental end-tidal CO_2-O_2 time history) can be specified to minimize the uncertainty in a parameter estimate.

The system incorporates three important features: (1) An on-line hybrid computing system for real-time data acquisition of human respiratory CO_2 response data, (2) A digitally-controlled breathing chamber in which the computer dictates the subject's inspired CO_2 concentration for the course of an experiment, and (3) A digitally-controlled breathing trainer to study the subject's voluntary interaction with his involuntray CO_2 response.

The digital computer dictates the subject's inspired CO_2 concentration for the course of an experiment. This flexibility allows us to design the dynamic variation in end-tidal CO_2 so that the experiment yields specific information about the properties of the human CO_2 regulator.

The digital computer also controls a device which generates a sound very similar to human breath sounds. By having a subject listen to this device and try to duplicate the breathing pattern being dictated by the computer, we can study the subject's voluntary interaction with his involuntary CO_2 response.

This system is presently in use in ongoing studies of the normal and drug-altered respiratory control system. A suggested application of this system is to improve dose-effect sensitivity and drug-effect specificity. Another application of the system could be for the study of exercise physiology.

IV. PROJECT DESCRIPTIONS: CORE RESEARCH AND MAJOR USERS

Drug Interaction Program

Name: Cohen, S. Project: DRUGALRT

Department: Clinical Pharmacology

Project Description: The project involves the establishment of a computer-based program aimed at preventing undesirable drug interactions and reducing drug toxicity at the Stanford University Medical Center. A data bank dealing with drug interactions of clinical significance will be compiled utilizing already available information present in the pharmacological literature. When prescriptions are filled by the Stanford pharmacists, the pharmacists will type the name of the drug and the dosage regimen into a terminal located in the Hospital pharmacy. When a new drug added to a patient's regimen interacts with any one of the several drugs the patient may already be receiving, the computer will print out an appropriate drug interaction alert accompanied by a literature reference, which will then be sent to the nursing unit by the pharmacist -- together with the drug. Prior to administering a drug accompanied by such an "alert", the nurse will contact the physician in charge, who will retain the prerogative of deciding whether or not the drug should be administered. This program will provide considerable teaching benefits to students and house staff, in addition to providing benefits of major importance to patient care. In addition, it will be possible to assess the impact of providing physicians with drug interaction information, and also to learn in a prospective way about the clinical consequences of drug interactions.

To date, a major part of data acquisition and programming has been completed. It is expected that the program will be operational on a trial basis during the next several months (April, May 1971).

In the future, it is anticipated that the program will be extended to other hospitals, and perhaps to non-hospital pharmacies in nearby communities. It is also expected that the program will interface with the laboratory test program which has recently been developed by Dr. Howard Sussman. Once this interface has been accomplished, it will be possible to utilize laboratory information in providing drug interaction alerts, and also to utilize prescription information in evaluating laboratory test results. Thus, laboratory evidence of inadequate renal function might serve to alert the physician not to administer usual doses of a drug that is excreted entirely by the kidney. Conversely, the artifactual effects of certain drugs on laboratory test results can be detected and appropriate warnings provided in the clinical laboratory.

IV. PROJECT DESCRIPTIONS: CORE RESEARCH AND MAJOR USERS

DENDRAL

Name: Reynolds, W., Ross, R., Stefik, M., and Stillman, R. (P.I.: Feigenbaum, E., Lederberg, J. and Djerassi, C.) Project: DENDRAL

Department: Chemistry and Genetics

Project Description: The DENDRAL project involves collaboration between the Instrumentation Research Laboratory operating under NASA grant NGR-05-020-004, investigators operating under NIH grant GM 00612-01, and ACME.

The emphasis of the DENDRAL-ACME efforts is computer science while that of IRL-ACME endeavors are data acquisition and computer-instrument control.

The DENDRAL project aims at emulating in a computer program the inductive behavior of the scientist in an important but sharply limited area of science, organic chemistry. Most of the work is addressed to the following problem: Given the data of the mass spectrum of an unknown compound, induce a workable number of plausible solutions, that is, a small list of candidate molecular structures. In order to complete the task, the DENDRAL program then deduces the mass spectrum predicted by the theory of mass spectrometry for each of the candidates, and selects the most productive hypothesis, i.e., the structure whose predicted spectrum most closely matches the data.

The project has designed, engineered, and demonstrated a computer program that manifests many aspects of human problem-solving techniques. It also works faster than human intelligence in solving problems chosen from an appropriately limited domain of types of compounds, as illustrated in the cited publications.

Some of the essential features of the DENDRAL program include:

- Conceptualizing organic chemistry in terms of topological graph theory, i.e., a general theory of ways of combining atoms.

- Embodying this approach in an exhaustive HYPOTHESIS GENERATOR. This is a program which is capable, in principle, of "imagining" every conceivable molecular structure.

- Organizing the GENERATOR so that it avoids duplication and irrelevancy, and moves from structure to structure in an orderly and predictable way.

The key concept is that induction becomes a process of efficient selection from the domain of all possible structures. Heuristic search and evaluation is used to implement this "efficient selection".

Most of the ingenuity in the program is devoted to heuristic modifications of the GENERATOR. Some of these modifications result in early pruning of unproductive or implausible branches of the search tree. Other modifications require that the program consult the data for cues (pattern analysis) that can be used by the GENERATOR as a plan for a more effective order of priorities during hypothesis generation. The program incorporates a memory of solved sub-problems that can be consulted to look up a result rather than compute it over and over again. The program is aimed at facilitating the entry of new ideas by the chemist when discrepancies are perceived between the actual functioning of the program and his expectation of it.

The DENDRAL research effort has continued to develop along several dimensions during this period. The mass spectra of some previously uninvestigated compounds were recorded. The computer program has been extended to analyze the mass spectra of a more complex class of compounds, using new kinds of data. The artificial intelligence work on theory formation and program generality has also progressed.

Many mass spectra were taken to gather more data for the DENDRAL Program. The analysis of the mass spectra of carbamates and methoxyoximes provided general mass spectrometry rules for the computer program. The spectra of many steroids were taken to elucidate the mass spectrometry of steroids and to provide data for a problem area new to DENDRAL.

The steroid problem is new in several respects: First, in working with steroids, the program deals with much more complex molecules than ever before; second, the computer program uses element maps from high resolution data to resolve ambiguities; and third, the program uses metastable peaks to determine parent-daughter relationships between ions and thus to distinguish molecular ions and their primary fragments. Programming for the preliminary analysis of steroid spectra is nearing completion, and will be useful in the laboratory even though the complete computer program for analyses of this complexity has not been finished.

The artificial intelligence interests of the DENDRAL group are reflected in recent work in program generality, partly described in reference (A), and in the program we call meta-DENDRAL described in reference (C), which will infer mass spectrometry rules from collections of data. Parts of the meta-DENDRAL program have been written which codify observations about mass spectrometry, and work has started on the succeeding phase of the program which will generalize these observations into tentative rules.

A. Feigenbaum, E.A., Buchanan, B.G., and Lederberg, J. "On Generality and Problem Solving: A Case Study Using the DENDRAL Program", in Machine Intelligence 6, B. Meltzer and D. Michie (eds), Edinburgh University Press, 1971.

B. Buchanan, G. and Lederberg, J. "The Heuristic DENDRAL Program for Explaining Empirical Data", to be presented at the 1971 Congress of the International Federation of Information Processing Society (August, 1971) and published by North Holland Publishing Co. (in press).

C. Buchanan, G., Feigenbaum, E.A., and Lederberg, J. "Beyond Heuristic DENDRAL", to be presented at the International Joint Conference on Artificial Intelligence (September, 1971) and published in the Proceedings.

An evaluation of new high performance mass spectrometers was carried out to plan new instrumentation for this program.

This system plans to incorporate a high degree of computer control. The goal of the instrumentation project will be to combine the analysis of the DENDRAL computer program with the data acquisition and control capability of the computer. It is planned to do a fast preliminary data acquisition, let the DENDRAL program determine what additional data and data mode is desirable, have the computer control the instrument mode and data scan, and return the pertinent data to the DENDRAL program. Further iterations of this cycle can be repeated as long as the sample persists.

It is planned to connect a GLC (gas chromatograph) to the inlet of the mass spectrometer. The persistence of a given sample is determined by the duration of a GLC peak, a few seconds to a very few minutes. The mass spectrometer of the kind we are considering could usefully take data in many modes; low, high, ultra-high resolution and meta stables, high or low ionization potential, etc. It cannot acquire all this data in the time span allowed by a single GLC peak. Hence it is required that the computer determine, during the limited sampling time the most useful mode of operation, and then implement this optimum mode.

Dispersed Computer System for Instrumentation-HIQ Terminal:

The project for development of dispersed computers is the HIQ (High IQ) terminal project being carried out in collaboration with Professor Melvin Schwartz of the Physics Department, with joint NASA support and Air Force support under contract AF F 44620 67C 0070. Professor Schwartz's interest concerned a Direct Memory Access (DMA) for a PDP-11. This forms an important portion of our "HIQ" terminal concept. This terminal development will provide the instrument-computer interface for the DENDRAL project.

The HIQ terminal is the result of an experience in connecting scientific instruments to various computers and the current supply of powerful but economical mini-computers. These computers have desirable attributes for dedicated real-time instrument interaction. However, when used alone they can require costly software developments. Current time-shared computers such as ACME have very efficient programming generating capabilities. In the present configuration the HIQ terminal utilizes a PDP-11 mini-computer. The mini-computer is tied to the ACME time-shared computer. The system facilities for the mini-computer will lie wholly in the larger time-shared computer: program manuscript editing, compiling or assembly, and the handling of files. All these functions benefit by the programming efficiency of the larger computer. In addition the time-shared computer replaces local tape and disc units.

By the end of 1970 the prototype HIQ using the PDP-11 as a Local Processing Unit was connected to ACME via our existing data lines. Program writing, code assembly, and a degree of control by ACME, the time-shared computer, has been achieved.

Next in development will be the use of the HIQ to preprocess data from the existing mass spectrometer data channels in our Chemistry Department (DENDRAL). After that we will integrate the Direct Memory Access (DMA) unit for use with the next generation of mass spectrometers, develop telephone line communication, and other "front end" modules.

Note: The following names and projects are associated with the DENDRAL project: W_REYNOL.DREAMS, W_REYNOL.DENDRAL, R_ROSS.CHEM, R_ROSS.DENDRAL, M_STEFIK.DENDRAL, R_STILLM.DREAMS, and R_STILLM.DENDRAL. They appear under categories 5 and 6 in the "Summary of Resource Usage Table".

IV. PROJECT DESCRIPTIONS: CORE RESEARCH AND MAJOR USERS

Mass Spectrometry

Name: Duffield, A. and Lederberg, J. (see Bacon, V. on Summary of Resource Usage table) — Project: GAME

Department: Genetics

Project Description: This project involves data analysis from a Finnigan 1015 mass spectrometer. In this on-line project, the decision-making capabilities of the computer are coupled with those of an operator to direct the operation of a Finnigan 1015 quadrupole mass spectrometer.

The computer is used to actively direct the operation of the mass spectrometer by controlling the mass filtering system of the instrument. It is used to recognize and control the voltage changes which define mass peaks and enable the rapid collection and presentation of data.

The computer traces out peak shapes of the known masses in a reference gas, allowing the operator to determine correct mass positions and to enter any shifts in calibration into the computer register for compensation automatically.

While taking data, the information may be displayed on an oscilloscope or recorded on magnetic tape. Once data is acquired, the structural identification of organic compounds is made from orthogonal coordinate or spiral base plots of mass spectra made by computer direction of a calcomp plotter. The system is also used to analyze gas liquid chromatograph effluent, permitting the structural identification of mixtures of organic compounds.

Stored data offer the future possibility of spectra matching of unknown compounds.

It is being applied to problems supported by both NIH Grant AM 12797-01 and NASA Grant NGR-05-020-004. Useful applications have been in the determination of optical purity of alcohols, ketones, phenylacetic acids and phenoxypropionic acids. This analytical technique has also been used to determine the absolute configuration of alloisoleucine present in the serum of a patient suffering from "Maple Syrup Urine disease". In addition chemical methods are being developed for the analysis of the basic and acidic constituents of urine. The bases are present in far smaller amounts than are the acids and the isolation of the former requires maximum sensitivity from the gas chromatography-mass spectrometry system. The computerization of this instrumentation aids in both the data collection and analysis.

IV. PROJECT DESCRIPTIONS: CORE RESEARCH AND MAJOR USERS

Clinical Laboratory Information System

Name: Sussman, H. Project: LABSYS

Department: Pathology

Project Description: A computer-based laboratory information system has been established at the Stanford University Medical Center. It is a modern system of handling the data flow in the clinical laboratories and has been developed on the ACME facility. Specific objectives of the system are to:

1) Reduce human errors;
2) Insure that processed data is available at a certain time each day;
3) Implement self-checking routines for monitoring accuracy of test results and to flag results that are beyond normal range;
4) Reduce bookkeeping and clerical work costs;
5) Provide wider distribution of data;
6) Improve procedural work flows as a step towards establishing a systems-oriented laboratory.

To date, the laboratory information system that has been developed handles the following functions of the clinical laboratory:

1) Ordering and processing of requests;
2) Accessioning of specimens into the laboratory;
3) Processing specimens within the laboratory for test analyses;
4) Recording test results both within the laboratory and externally.

All data is entered into the system by optical mark cards through a Hewlett Packard 21-2761B optical mark sense reader. These cards include cards to request that services be performed by the laboratory, cards to indicate the disposition of specimens within the laboratory, and cards to enter test results. ACME is used to control the process and report back information to the laboratory.

The first pilot study was conducted in the intensive care unit at the Stanford Medical Center. The logic of the system was tested and the operational commitments of the various staffs were determined. A current pilot study is being conducted using the entire Hoover Pavillion as a test model. In the next few months the gains of the automated laboratory system will be evaluated over the present manual system. The study is designed to allow an operations research type study of all transactions between the Hospital and the laboratory.

IV. PROJECT DESCRIPTIONS: CORE RESEARCH AND MAJOR USERS

Name: Sussman, H. Project: LABENG

Department: Pathology

Project Description: Four Electrical Engineering students are connecting one of the large instruments in the clinical laboratory to the IBM 1800 for data collection.

This project will further the establishment of a modern system of handling the data flow in the clinical laboratory. The software for such a system is largely developed using ACME, with test results being entered by means of cards.

A direct connection to the 1800 will enable results to be entered into the system without the high probability of error inherent in transcribing results onto cards.

IV. PROJECT DESCRIPTIONS: CORE RESEARCH AND MAJOR USERS

B. Major Users

Listed in alphabetic order by Principal Investigator are descriptions of a few of ACME's major user projects. Additional descriptions of projects using ACME are presented in Part IV of this report. All of the projects described here are charged for all of their use of ACME services.

The Biotechnology Resources Branch requested that the current year annual report include more descriptive material on a few of the major users' projects. We have selected the projects which follow with these criteria in mind: amount of usage, written material available, and varying types of usage of ACME. Dr. DeGrazia's work in Nuclear Medicine involves the use of a model, realtime data acquisition, and graphics terminals. The Immunology Project of Dr. Fries is an information retrieval project on a large data base. Dr. McConnell's project involves instrumentation that drives a plotter. ACME reads the X-Y coordinates via the 1800. Dr. Pauling's project involves realtime data collection of time series data from gas chromatographs, plotting of data and analysis. Dr. Petralli's work in the Infectious Disease Laboratory is an example of a production program currently used to ensure good quality control in the handling of laboratory samples. The Stroke Registry Project of Dr. John Wilson entails creation of a data base, manipulation of data, and report generation.

IV. PROJECT DESCRIPTIONS: CORE RESEARCH AND MAJOR USERS

Name: DeGrazia, J. Project: RADIOREN

Department: Nuclear Medicine

Project Description: Renogram data are analyzed with a kinetic model of renal function to determine whether (1) quantitative estimates of renal function parameters could be obtained and (2) advantage accrues from employing additional probes in performing hippuran renograms.

Four-probe renograms were performed on patients suspected of having renal disease. The sitting hydrated patient was given an intravenous bolus of I-131 hippuran. Four balanced probes, equipped with thick-walled collimators, continuously monitored activity over each kidney, the heart and the bladder. Data was obtained for thirty minutes directly through an IBM 1800 or recorded by audio tape.

Among the parameters derived are:

1) Effective renal perfusion, as a fraction of cardiac output;
2) Fraction of effective renal perfusion to each kidney;
3) Excretion rate constant for each kidney (a measure of tubular function);
4) Urine transport time for each collecting system (a measure of obstruction, dehydration, etc.).

The clinical value of parameter estimation is being evaluated and a comparison is being made between the two-probe analysis and that using four probes. Thus this is testing for improvement when areas of interest are used to form the data base. This program will be a model for diagnostic studies of other organs with radioactive isotopes.

IV. PROJECT DESCRIPTIONS: CORE RESEARCH AND MAJOR USERS

Name: Fries, J. Project: DATABANK

Department: Medicine - Immunology

Project Description: This project establishes a large databank of clinical information and explores multiple uses of such stored information. The databank currently includes 1,200 patient visits and approximately half a million individual items of data. A variety of search procedures operate on this body of data to give answers to clinical questions, provide administrative data, perform retrospective research procedures, coordinate and evaluate ongoing prospective clinical trials, and provide data for clinical correlations.

The project grew out of clinical problems in establishing significant clinical and laboratory correlations in immunologic diseases and assessing these correlations in regard to classification, pathogenesis, prognosis, and response to therapy. Diseases in this area are characterized by involvement of a large number of organ systems, a large variety of associated laboratory abnormalities, and a course long in duration and punctuated with periodic exacerbations and remissions. A massive amount of data is thus generated by each patient and meaningful correlations may be obscure to the clinician and inaccessible to the clinical researcher. The data cannot be well handled retrospectively under current systems nor can they be handled manually.

An orderly comprehensive method of recording patient data structured with respect to time has been developed and established. Information recorded in this manner has been stored in the databank. Using the databank as a central information processing vehicle, associated physicians in the community have become active in clinical research projects of the division and are obtaining significant clinical information relevant to management of their patients. In the early stages, therefore, a regional medical system of physicians interested in rheumatic disease is being established with an upgrading and a monitoring of the quality of care in the region. The system was developed for rheumatic disease but is easily applicable to any disease area or to general medicine itself. Other groups associating with the project are actively pursuing these ramifications. The availability of the databank has greatly enhanced the clinical program and has resulted in the establishment of clinical fellowships and additional student learning opportunities. The teaching value of available accessible clinical information cannot be overestimated and these applications are in daily use.

IV. PROJECT DESCRIPTIONS: CORE RESEARCH AND MAJOR USERS

Name: McConnell, H. Project: ABSORB

Department: Chemistry

Project Description: ACME is being employed for analysis of experimental paramagnetic resonance spectra and calculation of theoretical spectra. These paramagnetic resonance spectra arise from the application of the "spin label" technique to problems involving biological macromolecules. Biological problems which are currently being studied include cooperative oxygen binding to the protein hemoglobin and the relation of molecular orientation and motion to function in biological membranes and membrane model systems.

The paramagnetic resonance spectra that are obtained in spin label studies are recorded as the first derivative of an absorption curve. The area under the absorption curve is proportional to the number of spin labels giving rise to the signal. Spin label spectra give information on changes in conformation or motion of a macromolecule. Frequently, these changes are detected as a small change in the paramagnetic resonance spectrum. Quantitative measurement of these changes requires normalization of spectra from a series of experiments. ACME will be used to compute the double integral of the experimental spectrum and then to regenerate a normalized spectrum. Subtraction and addition of spectra will also be used to analyze experimental data. In addition, a program for generation of theoretically calculated spectra will be employed.

Name: Pauling, L. Project: MENTLRES

Department: Chemistry

Project Description: This project involves research on the molecular basis of mental disease. Samples of urine and breath are taken before and after a synthetic diet, and analyzed by gas chromatography for abnormal patterns. Computerization is necessary for collection and rapid analysis of large volumes of data, and the project has recently hooked into the ACME system. A small project on mental retardation has been run and future plans include a large study of schizophrenia with all analysis done within ACME.

IV. PROJECT DESCRIPTIONS: CORE RESEARCH AND MAJOR USERS

Name: Petralli, J. Project: MED_DATA

Department: Medicine - Infectious Diseases

Project Description: Antibiotic-sensitivity testing gives physicians important information about treatment of specific infections. The fact that the Food and Drug Administration recently decided to regulate the formulation of antibiotic-sensitivity disks reflects the increasing awareness of the critical nature of this testing procedure. To improve the quality of antibiotic-sensitivity data (high potency single disc method) and to guide the interpretation of results and antibiotic selection, a computer program has been developed. Clinical information and zone sizes are entered into the ACME computer each day. As the information is given to the computer, the quality-control program immediately detects and challenges unusual results and directs the laboratory technician to appropriate restudy of the organism in question. This system converts zone sizes to resistant, intermediate, or sensitive and prints final reports from its memory. Decreased potency of antibiotic disc is detected by comparison of periodically determined mean zone sizes. Limits of confidence of a single reading are established by review of zone sizes observed with a standard organism tested on different occasions. Knowledge of antibiotic sensitivities of organisms isolated from a specific site such as blood or urine will help to guide the selection of antibiotics before specific sensitivities are known. Such information is of value in selection of antibiotics in treating rarely encountered organisms with less well-known sensitivity patterns or in selection of alternate antibiotics when the first choice drug is hazardous. Yearly comparison of antibiotic sensitivity patterns obtained will give information about major trends and suggest appropriate changes in treatment of various infections.

Thus, a new weapon in the battle against disease has been developed -- a computer to keep tab on dangerous bacteria and to help select which antibiotic drugs should be used to treat infections. Through antiobiotic-sensitivity testing, the computer has completely eliminated errors in conversion from zone size to sensitivity, which otherwise occur once in every 12 reports.

In addition to improving the accuracy of laboratory results for the benefit of patients, the computer has proved valuable in checking the work of laboratory technicians and students undergoing training. With the initial goal accomplished, that of computer quality control of antibiotic-sensitivity testing, future plans call for the study of when and why organisms become resistant to antibiotics.

IV. PROJECT DESCRIPTIONS: CORE RESEARCH AND MAJOR USERS

Name: Wilson, J. Project: STROKE

Department: Regional Medical Program

Project Description: This project involves the development of a county wide registry on stroke patients for a period of one year. The goal is to develop a population base for study and analysis of descriptive parameters of stroke, correlations and relationships of parameters with resultant predictive output for improvement of treatment and care of patients.

To date, two programs have been written for input and storage of data on stroke patients in acute facilities. These can be used to update and correct data as well as in checking the accuracy of the data. Once the data has been input, two output programs can be run which give an evaluation of the patient's status upon admittance and discharge. For the period July 1, 1970 through February 28, 1971, data on approximately 300 patients has been stored in the computer file. Each month, data on 30-40 stroke patients is entered into this file via the teletype terminal located at the Dominican Santa Cruz Hospital. On the same terminal, evaluations of the patient's status on admission and discharge are obtained based on the computer data, and a printout of the data regarding the patient is placed in the patient's medical records. Preliminary statistical analysis (in the form of a monthly report) of the data obtained between July 1, 1970 and February 28, 1971 has also been completed.

Future plans include the continuation of data collection and processing. Enlargement of the stroke registry in the computer is anticipated to include data on long-term care of the stroke patient based on evaluations at three months, six months and a year after discharge from the acute facility. More sophisticated and definitive analysis of data will aid in improvement of care. Possible predictive relationships and correlations will be sought from the data.

V. USER CORE RESEARCH - FY1972

The user-related core research activities for the coming year will include the DENDRAL Program, Drug Interaction Program, Clinical Laboratory Data Collection and Analysis, Arrhythmia Detection, and other programs to be identified. Only the Arrhythmia Detection is a new project.

A. Current Core Research Projects

1. DENDRAL

ACME will be used to support DENDRAL over the next 12 to 18 months primarily by improving the LISP compiler and relating realtime services to DENDRAL needs. Some graphics support is contemplated for scanning search trees.

2. Drug Interaction Program

The Drug Interaction Program will continue but on new problems. The goal in FY1971 was to get prescription data into the system along with a patient census and to launch use of the system by the Pharmacy. For next year, Dr. Cohen is seeking a new grant for further work in relating drug interactions to more of the known factors about each patient (i.e., clinical lab data, admissions data).

3. Clinical Laboratory

Additional instruments in the laboratory will be connected to ACME for realtime data collection.

B. Proposed Core Research

1. Arrhythmia Detection

The Arrhythmia Detection System is planned as a joint effort between ACME and Dr. Don Harrison in the division of Cardiology. Dr. Harrison expects to use a small Hewlett-Packard computer as the control device for an arrhythmia detection system. The Hewlett-Packard computer would be connected to the ACME system for large file storage and data analysis. The detection system will be based largely on the work done at Washington University in Saint Louis by Dr. Jerry Cox and others, and will incorporate a number of new design concepts from a local group. This is viewed as the first step in a Cardiac Care Unit Monitoring Package.

V. USER CORE RESEARCH - FY1972

This project is included as ACME core research with the following conditions:

- This project is to be funded from ACME's income or otherwise as a cost above the basic budget of $800,000 in direct costs for FY1972.

- We are not attempting to compete with the study section review process. The basis for ACME's interest in this process is a future convergence of ACME's realtime goals with the overall Cardiac Care Unit Monitoring System.

At the present time the detection of arrhythmia depends upon two techniques:

- Analog devices that detect gross changes in heart rate.
- Visual EKG monitoring by trained nurses.

Neither of these techniques, alone or in concert, are wholly satisfactory. Devices that detect gross rate changes give an indication only after the patient has entered a life-threatening condition. By visual monitoring, trained nurses should be able to detect subtle arrhythmias which are often precursors to a life-threatening situation. However, it is obviously unrealistic to expect anything close to 100% effective visual monitoring. Limited attention span, fatigue, a number of tracings to watch simultaneously, plus the normal distractions of the CCU environment all vitiate the nurse's effectiveness.

What is needed is a technique that would be able to detect subtle arrhythmias and to provide constant monitoring.

This would be some sort of device that would be able to monitor EKG's on a beat-by-beat basis, detect the subtle arrhythmias that are precursors to life-threatening situations, and give an alarm that would allow a nurse to initiate proper treatment.

The heart of the arrhythmia monitoring system will be a high-performance mini-computer. The exact size of the computer, as well as the number of patients that can be monitored are yet to be determined. From past experience we expect to monitor 8 patients using a machine with an 8k memory. The execution speed of the machine is of critical importance since the number of patients monitored, and hence the cost-per-patient of the system, is primarily limited by this factor.

Input of EKG's to the system will be performed by a high-speed analog-to-digital converter. The analog-to-digital converter will interface to the normal central station cable connectors. Output of alarms will be augmented by additional alarm indicators to the normal central station alarm devices. This will allow for the normal operation of such devices as tape delays or graphics recorders.

2. Other Projects

Other core research applications will be identified in the course of the year. Potential candidates at this time include Dr. Eugene Dong's non-invasive arrhythmia detection system development, and some of Dr. DeGrazia's kidney function work in Nuclear Medicine. The principal investigator for ACME will issue new criteria for potential users to consider if they wish to become classified as ACME core research. Further discussions with NIH Biotechnology Resources Branch are needed on this subject.

3. Realtime Programs

We will attempt to expand the number of realtime users. These users have received a priviledged rate for ACME use because they have been pioneering a new area and are sharing the problem solving techniques developed with the community. As part of our move to become self-sufficient through fee for service, we expect to reduce the subsidy.

PART 3: UTILIZATION AND COST DATA

VI. BUDGET

A. Resource Expenditures

SUMMARY

		Total Resource Expenditures		
		Actual Previous Budget Period	Current Budget Period	Estimated Next Budget Period
1.	Personnel:			
	a. Salaries & Wages	201,673	237,973	247,735
	b. Fringe Benefits	24,710	32,942	37,384
	Subtotal	226,383	270,915	285,119
2.	Consultant Services	1,500	800	1,000
3.	Equipment:			
	a. Main Resource-Rented	367,394	375,254	365,825
	b. Main Resource-Purchased	27,453	39,251	61,136
	c. Supporting Equipment	10,876	10,120	8,382
	d. Equipment Maintenance	4,225	6,559	8,670
	Subtotal	409,948	431,184	444,013
4.	Supplies	12,939	13,500	16,250
5.	Travel	3,896	3,600	4,000
6.	Engineering Services	20,508	17,810	30,000
7.	Publication Costs	4,262	4,000	4,000
8.	Other			
	a. Computer Services (1)	12,177	9,660	7,000
	b. Other	7,915	7,900	8,618
	Subtotal	20,092	17,560	15,618
9.	Subtotal - Direct Costs	699,528	759,369	800,000 (3)
10.	Indirect Costs (2)	114,954	140,404	171,598
11.	Total Costs	814,482	899,773	971,598

(1) Includes IBM education courses

(2) Based on salary and wages in years 04 and 05; based on net ($800,000 - equipment rentals and purchases totalling $428,077) total direct costs in year 06 (will be reduced by netting revenue from service fees from direct costs)

(3) This budget level does not include the efforts we would like to fund using ACME's income. For example, see estimate for arrythmia detection work on page 52.